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February 1, 2005

BY HAND DELIVERY AND BY E-MAIL

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0454, FDA Notice titled "Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications; Public Meeting"

Dear Sir or Madam:

Hyman, Phelps & McNamara, P.C. submits these comments on behalf of clients who are manufacturers and marketers of dietary supplements. The Food and Drug Administration (FDA) published the Notice referenced above on October 20, 2004. 69 Fed. Reg. 61680. FDA's Notice represents FDA's first formal effort to seek industry input as to the statutory, regulatory and policy issues that apply to new dietary ingredients (NDIs).

The statutory provision relating to NDIs, 21 U.S.C. § 350b, has been in place since October 15, 1994, the date that the Dietary Supplement Health and Education Act of 1994 (DSHEA) became effective as an amendment to the Federal Food, Drug, and Cosmetic Act (FDC Act). Industry practices have developed and have become established around this statutory provision, and, given that more than ten years have passed, these practices deserve to be recognized and accepted, and in some cases adopted, as the authoritative standard for the dietary supplement industry.

2004N-0454 C20

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As a result of the public meeting on November 15, 2004, FDA indicated that the agency recognized the need to treat the October 20, 2004 NDI Notice as a first step in a longer dialogue with industry and that FDA would not attempt to issue draft guidance to industry based on this first round of comments. That is a necessary conclusion given the concerns that were expressed at the public meeting.

First and foremost, FDA should agree to focus on the broader issues that pertain to NDI regulation, rather than attempt to define specific "requirements" for NDI notifications, as it appeared from the NDI Notice FDA was attempting to do. Industry is understandably concerned that FDA will try to make the NDI notification process as much like a pre-market approval process as possible. Everyone at FDA who is involved in NDI policy decisions must understand that it was FDA's excessively restrictive attempts to regulate dietary supplements as "food additives" under the FDC Act that led to DSHEA, and that the NDI process was part of a larger legislative effort to clarify that Congress never intended FDA to have premarket approval authority over dietary supplements.

Consistent with other provisions in DSHEA, the NDI process clearly places the primary responsibility for product safety in the hands of industry, not FDA. Industry, not FDA, compiles the information needed to reach a conclusion that an NDI "will reasonably be expected to be safe." 21 U.S.C. § 350b(a)(2). DSHEA's NDI provision requires that, for a certain limited category of NDIs, FDA receive the information that the manufacturer of an NDI has compiled 75 days prior to marketing, nothing more. Id. No action on FDA's part is required for industry to fulfill the NDI requirements.

If FDA disagrees with the manufacturer's conclusion that the information supplied is sufficient to meet the "reasonably . . . expected to be safe" standard, there is no violation of the NDI provisions or any other provision of the FDC Act. Nonetheless, FDA can protect the public from any potentially unsafe NDIs by taking one of several enforcement actions within the 75-day notification period prior to product marketing, including initiating a seizure action against the product containing the NDI pursuant to 21 U.S.C. § 342(f). In such an action, FDA would have the burden of proving, among other things, that the marketer of the NDI that was the subject of the notification to FDA did not provide FDA with sufficient information to show that the NDI met the "reasonably . . . expected to be safe" standard. 21 U.S.C. § 342(f)(1)(B).

In sum, as these comments discuss in more detail, FDA needs to develop any policies relating to NDIs with extreme care and after thorough discussion with the affected industry, which has already developed and established extensive business practices based

on over a decade of interpretation of DSHEA's NDI provision. FDA should interpret the NDI provisions broadly to assure wide consumer access to safe and beneficial dietary supplement products.

I. HISTORY SHOULD NOT BE REPEATED

Given the length of time since the passage of DSHEA, and normal turnover within the agency, there is understandably concern that FDA personnel responsible for considering agency policy with respect to NDIs are unfamiliar with the problems that led to DSHEA. This concern has been significantly strengthened in light of the very detailed questions FDA has posed in the NDI Notice pertaining to the types of data that FDA appears to believe might be necessary to satisfy the agency that the "reasonably . . . expected to be safe" standard has been met. In short, there is concern that FDA has forgotten the history leading to DSHEA and is once again creating a food additive type of review process for NDIs. Therefore, revisiting FDA's past regulatory policies is an essential first step to the development of any new NDI policies.

FDA interpreted the FDC Act in the 1980s and early 90s as requiring FDA pre-market approval of a food additive petition for virtually all dietary ingredients other than traditional vitamins and minerals. FDA effectively blocked market access for non-traditional dietary supplements by both refusing to approve dietary supplement food additive petitions and threatening or initiating seizure actions against products that did not fit FDA's "traditional" mold.

In the process of enforcement, FDA made arguments that were irrational from both a legal and scientific perspective. Two products, evening primrose oil (EPO) and black currant oil (BCO), both marketed as sources of gamma linolenic acid (GLA), became the focus of litigation over the application of the food additive provisions to dietary supplements. In the end FDA's misuse of the food additive requirements to restrict the supplement market to traditional vitamins and minerals led to the passage of DSHEA.

A. The EPO Litigation

In 1985, FDA issued an Import Alert for EPO.[1] The alert instructed FDA officials to detain EPO labeled for food use because the agency considered it an unsafe food additive. In 1988, the dietary supplement manufacturer Efamol, based in the United Kingdom,

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[1] See FDA, Import Alert No. 66-04: Oil of Evening Primrose (1985).

initiated discussions with FDA regarding the procedure for obtaining FDA affirmation, through the existing petition process, of the status of EPO as generally recognized as safe (GRAS). However, before a GRAS affirmation petition was filed, FDA initiated two seizure actions of Efamol's EPO products alleging, among other things, that EPO was not GRAS and was, therefore, an unapproved food additive.[2]

In this litigation, FDA argued in part that EPO could not be GRAS because EPO might cause cancer, birth defects, hydrocephalus in newborns, convulsions, immunosuppression, and excessive bleeding, and that it was also unsafe because it contained pesticides and toxic oxidative byproducts.[3] FDA made these arguments even though supplements containing EPO were then and are now widely sold worldwide and on the U.S. market, with virtually no reports or other evidence of adverse effects. There have been no renewed claims of FDA concern post-DSHEA.

The Ninth Circuit upheld a district court ruling that EPO was not GRAS, illustrating the difficulty that the GRAS standard posed for even the safest dietary supplements pre-DSHEA.[4] Demonstrating the resources that FDA was willing to expend to keep the dietary supplement market free from non-traditional products like EPO, soon after the Ninth Circuit issued its ruling, FDA awarded the Commissioner's Special Citation to 61 FDA personnel, who comprised the "Evening Primrose Oil Litigation Team."[5]

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2 See United States v. 45/194 kg. Drums of Pure Vegetable Oil, No. CV 89-73, 1989 WL 248572 (C.D. Cal. Nov. 30, 1989), aff'd, (9th Cir. 1992); United States v. 21 Drums of Food and Drug, 761 F. Supp. 180 (D. Me. 1988).

3 See FDA Expert Declarations, 45/194 kg. Drums of Pure Vegetable Oil (C.D. Cal 1989).

4 See 45/194 kg. Drums of Pure Vegetable Oil, 961 F.2d 808.

5 Dietary Supplements, Before the House Committee on Appropriations, Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, 103d Cong. 208 (1993).

B. The BCO Litigation

FDA's two seizure actions against BCO products involved dietary supplement products consisting of pure oil extracted from black currant seeds.[6] FDA alleged in both cases that BCO was not GRAS and was, therefore, an unapproved food additive. However, the initial issue for the courts in the BCO case was whether BCO was a pure, single ingredient food that FDA was not authorized to regulate under the FDC Act "food additive" provisions. If the "food additive" provisions were not implicated, then whether BCO was GRAS was irrelevant.

FDA argued that the addition of BCO to a gelatin capsule caused the BCO to become a "food additive" within the meaning of the FDC Act and that as a "food additive," the substance could not be marketed as a dietary supplement without first applying for and obtaining FDA approval of a "food additive" petition.[7] The U.S. Court of Appeals for the Seventh Circuit, in a unanimous three-judge opinion, stated as follows:

> The only justification for this Alice-in-Wonderland approach [i.e., FDA's "food additive" allegation] is to allow the FDA to make an end-run around the statutory scheme . . . . [W]e hold that [BCO] encapsulated with glycerin and gelatin is not a food additive . . . . FDA has not shown that [BCO] is adulterated or unsafe in any way.[8]

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6 United States v. Two Plastic Drums . . . Viponte Ltd. Black Currant Oil, 984 F.2d 814 (7th Cir. 1993); United States v. 29 Cartons of . . . an Article of Food, 987 F.2d 33 (1st Cir. 1993). The product at issue in the EPO litigation was EPO to which vitamin E had been or was to be added as a preservative. The Ninth Circuit distinguished the EPO cases from the BCO cases on this basis. See 45/194 kg. Drums of Pure Vegetable Oil, 961 F.2d 808.

7 See Two Plastic Drums, 984 F.2d at 816; 29 Cartons of . . . an Article of Food, 987 F.2d at 36.

8 Two Plastic Drums, 984 F.2d at 819-20.

The U.S. Court of Appeals for the First Circuit, also in a unanimous three-judge opinion, ruled similarly to the Seventh Circuit:

> FDA's reading of the [FDC] Act is nonsensical . . . . The proposition that placing a single-ingredient food product into an inert capsule as a convenient method of ingestion converts that food into a food additive perverts the statutory text, undermines legislative intent, and defenestrates common sense. We cannot accept such anfractuous reasoning.[9]

Congress concluded that unless it stepped in and passed DSHEA, FDA would continue to try to prohibit the marketing of safe and proper dietary supplements through illegal means:

> Although a fair reading of the current statute [i.e., the "food additive" provisions of the FDC Act], as most recently interpreted by two United States courts of appeal, should make . . . amendment [of the FDC Act by DSHEA] unnecessary, the committee has heard testimony that the FDA has rejected these [judicial] holdings. The committee is therefore concerned that the FDA will persist in such litigation, and thereby continue to subject small manufacturers to the choice of abandoning production and sale of lawful products, or accepting the significant financial burden of defending themselves against baseless lawsuits [brought by the FDA].[10]

The sentiment expressed in this Senate Report and the courts' opinion, and the extreme hostility that FDA's overreaching caused among consumers, led to the passage of DSHEA by unanimous vote in both the House and the Senate.

C. FDA Must Resist Any Tendency to Create a New "Approval" Process

FDA should now accept the reality of DSHEA, and to the extent that new policy is developed for NDIs, should interpret the terms of the FDC Act broadly to place the primary responsibility for safety of NDIs on industry's shoulders, as Congress intended, and to permit market access where industry has compiled the safety information necessary to meet

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9 29 Cartons of . . . an Article of Food, 987 F.2d at 37, 39.

10 S. Rep. No. 103-410, at 21 (1994).

the "reasonably . . . expected to be safe" standard. FDA's authority to restrict access to the market derives not from the NDI provisions, but from the enforcement provisions of the FDC Act, including 21 U.S.C. § 342(f), which authorize FDA to keep unsafe products from reaching the market where NDI notifications are insufficient, to remove any unsafe products from the market, and to initiate other enforcement actions, including injunctions and even criminal prosecution, to assure that all dietary supplements are safe.

II. FDA SHOULD RESTRICT ITS FOCUS TO BROAD NDI POLICY ISSUES

FDA's NDI Notice contains questions that FDA has asked interested parties to answer. Some of these questions relate to broad policy issues that are appropriate to this first round of discussion on NDI issues. However, the bulk of the questions, particularly those pertaining to "Chemical Identification of the NDI," "Establishing a Reasonable Expectation of Safety" and "The Role of Definitions in Evaluating NDIs" in Sections IV. B., D. and E. of the Notice, are unnecessary in light of DSHEA's focus on industry responsibility for assuring product safety and given the minor role that the NDI notification process plays in the ultimate scheme of FDA's regulatory overview of dietary supplements.

Again, the law is clear. According to the FDC Act, 21 U.S.C. § 350b(a)(2), in the limited cases where an NDI notification is required, all that the manufacturer or distributor of an NDI needs to do to comply with the NDI notification requirement is to file a notification, with the information that the manufacturer or distributor deems adequate to establish that the NDI meets the "reasonably . . . expected to be safe standard," 75 days prior to introducing or delivering the product containing the NDI into interstate commerce. The 75-day notice permits FDA to take enforcement action if needed prior to marketing, if FDA disagrees.

If industry decides to develop criteria for meeting the "reasonably . . . expected to be safe" standard, that should be done. Any FDA effort to establish detailed requirements for meeting the "reasonably . . . expected to be safe" standard would exceed the authority granted by the FDC Act.

A. FDA Should Interpret § 321(ff) Broadly to Permit a Wide Range of "Dietary Ingredients" in Dietary Supplements, as Congress Intended

The first question that FDA has asked in section IV.A. of the NDI Notice is:

What should FDA consider to determine whether a substance falls within a particular category of the statutory definition of "dietary ingredients" under sections 201(ff)(1)(A) though (F) of the act?

69 Fed. Reg. at 61682. Simply put, FDA is asking the wrong question.

FDA has misinterpreted section 201(ff)(1) as a "definition" of the term "dietary ingredient." That is incorrect. This section is a definition of the term "dietary supplement," which as part of that definition, includes a list of different types of acceptable dietary ingredients. This list purposefully includes both ingredients that FDA accepted as dietary supplement ingredients prior to DSHEA, such as vitamins and minerals, and ingredients that FDA had historically tried to keep off the market as illegal "food additives," such as herbs or other botanicals. Most important, to make it clear that ingredients such as EPO, BCO and many other ingredients that do not fall into any particular category are appropriate "dietary ingredients" for dietary supplements, Congress added sections 201(ff)(1)(E) and (F), 21 U.S.C. §§ 321(ff)(1)(E) and (F). Subsection (E) includes "dietary substances" in the list of "dietary ingredients," and subsection (F) includes any "concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)." Therefore, section 201(ff)(1) does not put restrictions on which "dietary ingredients" might be used in "dietary supplements," but rather was intended to make it clear that any "dietary ingredient" not otherwise prohibited, such as for reasons of safety, was appropriate for use in dietary supplements.

FDA has stated in letters responding to NDI notifications that section 201(ff)(1)(E) applies only to dietary ingredients commonly used in human food or drink. FDA's position would render many widely marketed and popular dietary supplements, including EPO, BCO, glucosamine, chondroitin and coenzyme Q10, to name a few, illegal because they do not meet the narrow interpretation of section 201(ff)(1) that FDA has expressed in its letters. This position is illogical, is contradicted by the express intent of DSHEA, and has already been challenged in an April 8, 2004 citizen petition filed by the Coalition to Preserve DSHEA (FDA Docket No. 2004P-0169). Other than an October 7, 2004 letter to the Coalition stating that FDA has been unable to respond in the required 180 days, FDA has yet to answer this petition.

FDA's effort to use section 201(ff)(1) as a means of restricting market access should be dropped. Therefore, FDA should not proceed further with any effort to answer question 1 in section IV.A. of the NDI Notice, or to define the terms contained in section 201(ff), as section IV.E. indicates that FDA might attempt to do.

B. FDA Should Treat Existing Lists of "Old" Dietary Ingredients as Authoritative

DSHEA defines the term "new dietary ingredient" as "a dietary ingredient that was not marketed in the United States before October 15, 1994, and does not include any

dietary ingredient which was marketed in the United States before October 15, 1994." 21 U.S.C. § 350b(c). Since the passage of DSHEA, industry and its trade associations have used a number of sources of information to establish which ingredients were "marketed" prior to October 15, 1994, including Herbs of Commerce (1992 American Herbal Products Association), and have worked to compile lists of "old" dietary ingredients. The result has been the stabilization of an industry practice of reliance on a variety of sources for pre-DSHEA marketing.

FDA now asks in the NDI Notice "[w]hat should FDA consider to determine whether a dietary ingredient was not marketed in the United States before October 15, 1994 and is therefore an NDI?" 69 Fed. Reg. 61682 (question 3, section IV.A.) (see also question 6 in this section concerning an "authoritative list"). FDA should not devote significant resources to answering this question but should instead serve as a support to the current process that industry is already using. Ultimately, consistent with DSHEA's allocation of responsibility for ingredient safety to industry, it should be left to industry to continue to refine current lists of "old" dietary ingredients, to the extent that is necessary.

Of course, FDA has the authority to act should the agency disagree. However, because the failure to file an NDI notification is easily remedied, ingredient safety, rather than an ingredient's status as a "new" or "old" ingredient, is the most important issue. This fact argues against FDA expenditure of resources to challenge or change the existing system for determining old versus new ingredients.

In short, both FDA and industry have long treated existing lists and other information on pre-DSHEA marketing as authoritative, and there is no compelling reason that this practice should be changed. FDA should rely on regulatory and enforcement actions based on lack of safety under applicable standards to accomplish the goal of keeping unsafe products from the market, rather than challenge established practices under existing interpretations of the NDI provisions.

C. FDA Should Accept the Existing Interpretation of "Present in the Food Supply" as Policy to Avoid Requiring NDI Notifications for Food Constituents

DSHEA provides an important exception from the NDI notification requirement. According to 21 U.S.C. § 350b(a)(1), a dietary supplement that contains an NDI is not adulterated if "[t]he dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." Industry has adopted a common-sense interpretation of this provision that reflects the clear intent of the statute – if humans are exposed to dietary

ingredients because they are naturally present in the food supply, then there is no reason to require FDA notification, as the safety of the ingredient will be adequately assured. Whether the ingredient is actually extracted from food, or is chemically synthesized to be identical to an ingredient in food, makes no difference either from a safety standpoint or in meeting the terms of this provision. If FDA develops any interpretations of this provision, FDA should again move carefully to preserve the broad intent of DSHEA and DSHEA's allocation of responsibility for safety to industry, and should avoid disrupting long-term industry practices.

D. FDA Should Not Attempt to Set Criteria for "Acceptable" NDI Filings, Other Than Very General "Content" Criteria

In addition to creating a unique premarket notification process for a limited class of NDIs, DSHEA established a unique safety standard for NDIs – NDIs must "reasonably be expected to be safe." 21 U.S.C. § 350b(a)(2). There is no recognition or discussion of this unique safety standard in FDA's NDI Notice. Instead, the Notice is substantially devoted to listing detailed safety criteria and data types that are equivalent to and in some cases exceed requirements for GRAS substances or for food additive approvals. It appears from the NDI Notice that FDA intends these extensive criteria to be established as a test that all NDI submissions should meet. This effort to establish detailed criteria for NDI submissions is inconsistent with DSHEA and should be abandoned.

FDA should accept and recognize Congress' intent to establish a unique notification process for a limited category of NDIs, as well as a unique and less-demanding safety standard than either the GRAS or food additive standards for foods. Creating criteria for NDI notifications, if they are needed, should be left to industry. This would be consistent with the overall NDI scheme, which places primary responsibility for safety on industry, with powerful enforcement tools in the hands of FDA to discourage inadequate safety reviews prior to ingredient or product marketing.

III. CONCLUSIONS

FDA must step back and recognize the intent of DSHEA to create a unique, limited review of a subcategory of NDIs under a less stringent safety standard than is required for food products that are regulated under the FDC Act's GRAS and food additive provisions. FDA's Notice has understandably created concerns that FDA is applying unreasonable interpretations to DSHEA that could block the marketing of safe and beneficial dietary supplements, similar to the FDA actions that led to DSHEA.

FDA should accept that DSHEA has created a system for NDI review that places primary responsibility for NDI safety on industry. FDA has limited powers of review but extensive enforcement tools should the agency disagree with industry assessments of safety. It is through use of these enforcement powers, not by narrow interpretations of the NDI and related FDC Act provisions, that Congress intended FDA to act to prevent the marketing of any products that might present a public health threat. By implementing DSHEA according to Congress' intent, FDA will have prior notice of the marketing of all potentially unsafe NDIs and will have ample time – 75 days – to act prior to marketing if FDA decides to challenge any NDI notification.

Thank you for the opportunity to provide comments on this important issue.

Sincerely,

A. Wes Siegner, Jr.

AWS/rd